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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,789	08/25/2003	Daniel P. Wermeling	05061447	2016

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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,789	WERMELING, DANIEL P.	
	Examiner	Art Unit	
	Timothy E. Betton	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,10-13,16-20 and 46-72* is/are pending in the application.

4a) Of the above claim(s) *1-4,7,8,10-13,16-20 and 46-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse in the reply filed on 6 November 2006 is acknowledged.

Election of Species

Applicant hereby elects claim Group III without traverse. Applicants further elect claim 72 as the species to be initially examined. Claims 53-72 read on this species. Claims 1-4,7,8, 10-13, 16-20, 46-52 are hereby withdrawn. Claims 5,6,9,14,15, and 21-45 are hereby cancelled.

Claim Rejections- 35 U.S.C. 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 53-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 53 discloses the phrase, " the spray plume has a maximum droplet size of about 2.2 to about 2.4 [micro] m." The disclosure seems to suggest that the [micro] m unit designation is directed only to the alleged 2.4 range and not to the alleged 2.2 range. A proper disclosure may be "2.2 [micro]m to about 2.4 [micro]m if that is the intended designation by applicant.

Instant claims 54 and 62-70 are identical to independent base claim 53 in that the first alleged range is void of any unit of measure in comparison to the alleged ending

range. For example, instead of "2.0 to about 2.2 cm", the modification, " 2.0 cm to about 2.2 cm" is proper.

Instant claims 71 and 72 are dependent from independent claim 53 and are therefore also rejected for the reasons disclosed above.

Claim 54 recites the limitation "the butorphanol" in relation to dependence from independent base claim 53. There is insufficient antecedent basis for this limitation in the claim. " The butophanol" disclosure suggests that mention was adequately disclosed in independent claim 53. Instant claim 53 only discloses the genus opioid, with no specific opioid disclosed in instant claim 53.

Instant claim 55 is also rejected based upon its dependence from instant claim 54.

The instant claim 65 discloses, "the spray plume has a span of about 1.55 to about 1.91. Likewise, instant claim 70 discloses, " the spray plume has a span of about 1.5 to about 1.9." There is no indication of units in order to determine the measure, order, or degree, which renders the cited claims indefinite. The two respective disclosures are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

It is unclear whether instant claims 65 and 70 are drawn to specific units disclosed in prior claim 63. Applicant must specify the scope of measurement for the ranges in subject claims 65 and 70.

Claims 63, 64, 68, and 69 recite the limitation "Dv: 10 and 50", respectively. There is insufficient antecedent basis for this limitation in the claim.

Instant claim 1 discloses no sufficient explanation or definition of the alleged value "Dv". The specification vaguely suggests on page 10 of revised version that there is a direct relation of this value to "mean span" or "droplet size distribution." Additionally, in the applicants' originally filed specification, the term distribution volume is disclosed in reference on page 27, however, there is no suggestion in the instant specification of this having any relation to the alleged value "Dv".

Claim Rejections- 35 U.S.C. 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

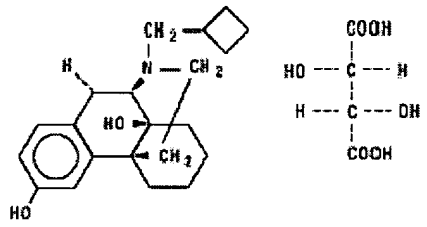
Claims 53-59 and 62-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstein et al. (USPN 5437267) and Levin, B. (PGPUB US 2001/0004644 A1) in view of Ward-Smith, S., (Semi-automated testing of nasal sprays. (Nasal Spray Testing, Pharmaceutical Technology Europe, (2002), pages 1-9).

For exemplary purposes, applicant discloses butorphanol tartrate in instant claims 54 and 71 which has an intranasal delivery formulation device system called Stadol NS®, Bristol-Myers Squibb in 1991 was approved by the FDA for marketing as a

prescription medication (A Brief History of Bristol-Myers Squibb, 2007, Newsroom, page 3, 8th paragraph).

Additionally for exemplary purposes:

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl) morphinan-3, 14- diol [S-(R*, R*)] - 2,3 - dihydroxybutanedioate (1: 1) (salt). The molecular formula is C21H29 NO2,C4H6O6, which corresponds to a molecular weight of 477.55 and the following structural formula:



Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl) morphinan-3, 14- diol [S-(R*, R*)] - 2,3 - dihydroxybutanedioate (1: 1) (salt). The molecular formula is C21H29 NO2,C4H6O6, which corresponds to a molecular weight of 477.55 and the following structural formula:

Butorphanol tartrate is a white crystalline substance. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

STADOL NS (butorphanol tartrate) is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Each bottle of STADOL NS contains 2.5 mL of a 10 mg/mL solution of butorphanol tartrate with sodium chloride, citric acid, and benzethonium chloride in purified water with sodium hydroxide and/or hydrochloric acid added to adjust the pH to 5.0. The pump reservoir must be fully primed (see PATIENT INSTRUCTIONS in HOW SUPPLIED) prior to initial use. After initial priming each metered spray delivers an average of 1.0 mg of butorphanol tartrate and the 2.5 mL bottle will deliver an average of 14–15 doses of STADOL NS. If not used for 48 hours or longer, the unit must be reprimed (see PATIENT INSTRUCTIONS in HOW SUPPLIED). With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8–10 doses of STADOL NS depending on how much repriming is necessary. (RXLIST monograghs; The Internet Drug Index, (2007), Butorphanol Tartrate; Description, pages 1 and 2). Above reference discloses general specifications which is obvious over the subject matter in applicant's invention in that an opioid intranasal delivery device is taught with ingredients that are not identical but contain similar constituents as disclosed in instant claims.

Weinstein et al. teach a device for the intranasal delivery of a medicament regimen to the nasal membranes for the treatment of such conditions as rhinitis (Abstract). Referenced Figure 1A depicts a perspective view of another embodiment of invention including 2 (in comparison to 1 or more claimed in instant claim 53) medicament canisters/chambers. The term chamber is interchangeable with the term vessel of instant claim 53. All other depictions for Figures 2 through Figure 7 incorporate

the use of more than two medicament canisters with variations in configuration thereof for optimal therapeutic delivery (Drawing sheets 1-3, columns 3-8).

Weinstein et al. does not teach use of opioid formulation in referenced device. Additionally, Weinstein et al. does not teach a description of spray plume actuation, the detection of droplet size distribution, or a specific droplet size.

Levin teaches the practicing methods comprising intranasally administering to the patient a pharmaceutical composition comprising a local anesthetic. Levin further discloses butorphanol tartrate for use in intranasal device for muscular headaches (page 2, section [0018]; page 21, section [0200]; page 39, claim 24).

Levin does not teach a description of spray plume actuation, the detection of droplet size distribution, or a specific droplet size. However, the examiner refers to Ward-Smith, which teach nasal spray formulations consist[ing] of the drug suspended or dissolved in an aqueous medium, which is filled into a bottle with a metered spray pump. Pump actuation by the patient delivers the drug in fine droplets into the nasal cavity. The pump is an integral part of the whole assembly and plays a crucial role in delivering an accurate dose to the correct absorption site. Of particular importance is the droplet size distribution produced by the pump, which must be optimized to increase nasal deposition and minimize lung deposition or absorption in the gastrointestinal tract (page 1, 1st paragraph). Further, Ward-Smith encompasses the spray droplet size ranges disclosed by instant claims with a description of the Spraytec with Nasal spray Actuator with a 200mm Fourier lens, [which] is [...] most typically used in this application, allowing measurements in the 1-400 [micro]m size range. This more than

adequately encompasses and is obvious over instant claim 53 which discloses a maximum droplet size of about 2.2 to about 2.4 [micro]m.

Further, Ward-Smith teaches the measurements at three different distances between the laser diffraction measurement zone and the tip of the pump (measurements of 3,6, and 9 cm) (page 3, Experimental, 4th sentence). Independent claim 53 and dependent claims 62-70 discloses a positioning of the device 1 cm and 5 cm away, respectively from a laser detection pathway. Ward-Smith teaches nasal spray formulations consist[ing] of a drug suspended or dissolved in an aqueous medium same as disclosed in instant claim 58. Laser diffraction as a technique for particle sizing is taught (page 2 and 3, Droplet sizing using laser diffraction). Multiple measurements are required for each measurement point to assess the measurement precision. The 10th, 50th and 90th percentiles (Dv10, Dv50 and Dv90) must be reported for the size distributions measured during each stage. The span of the size distribution must also be reported (Span = [Dv90 - Dv10/Dv50]) according to Ward-Smith et al. (pg 3, Experimental, 5th sentence). Instant claims 63, 64, 68, and 69 are obvious in view of Ward-Smith. Referenced page 6-8 teaches actual result data obtained for manual actuation pumps and as a function of pressure (semi-automated) pumps. The reference discloses ranges higher in comparison to instant claimed ranges with the exception of some examples of conclusive data. One of ordinary skill in the pertinent art would at once recognize the necessity to properly adjust the ranges.

It, therefore, would be prima facie obvious to modify the device and medicament administered in Weinstein et al. to an opioid. Accordingly, it would be obvious to modify

the device of Levin, which does teach a practicing administration of butorphanol tartrate in an intranasal device. The motivation to combine would be obvious based in view of Ward-Smith, which does teach the specific parameters of efficacious administration, i.e., description of spray plume actuation, the detection of droplet size distribution, specific droplet size, etc.

Claims 60, 61 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum et al. (Intranasal Delivery of Morphine, The Journal of Pharmacology and Experimental Therapeutics, 2001,vol.301, no.1, pages 391-400), Pezron et al. (Prodrug strategies in nasal drug delivery, Expert Opin. Ther. Patents (2002) 12(3): 331-340), and Manjushree et al. (Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients, CAN J ANESTH 2001,49:2, pages 190-193) in view of Midha et al. (USPN 6127385)

Illum et al. teach the intranasal delivery of morphine, a potent narcotic analgesic, [which] produces a variety of pharmacological responses by interacting with the opioid receptors in the nervous system (page 391, 1st paragraph). Further, Illum et al. teach butorphanol as a practicing analgesic agent that can be effectively and rapidly absorbed from the nasal cavity (page 391, 3rd paragraph). Additionally, Illum et al. teach a pH range of 4.02 and 3.81, respectively which are specific to the broad pH range (pH of about 3 to about 6) disclosed in instant independent claim 53 (page 392, Formulation Preparation, 2nd and 3rd paragraph).

Illum et al. does not teach the intranasal opioid formulation with citrate buffered water or a sweetener. Illum et al. teach said formulation with an absorption-promoting agent such as chitosan.

Pezron et al. teach strategies for enhanced nasal drug delivery via taste modification of these bitter moieties by use with moieties that lack bitterness (page 337, Miscellaneous applications, 2nd paragraph).

Pezron et al. does not teach nasal drug formulation with a sweetener to mask the bitter taste due to administration.

Manjushree et al. teach the well-established use of the intranasal opioid fentanyl with the nasal carrier citrate in the formulation (page 191). Further, Manjushree et al. teach the scope of prolonged use of fentanyl citrate without any adverse effects. Manjushree et al. does not teach an intranasal opioid with a sweetener or flavoring agent.

However, the Examiner refers to Midha et al., which teach an embodiment of a nasal formulation containing [active agent] dissolved in aqueous or non-aqueous solvent, an antioxidant and aromatic oils as flavoring agents (column 4, lines 59 to 63). In instant claim 61, aromatic oils are disclosed as rosemary oil, spearmint oil, thyme oil, etc. Instant claim 72 specifically discloses sucrose, but Midha et al. does not teach sucrose. However, it would have been obvious to interchange flavoring agents based on the list disclosed within instant claim 61.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ardin H. Marschel 1/4/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

TEB